CLAIMS

1. A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising:
co-administering to the mammal, a virus in an amount sufficient to deplete or inhibit at least some antigen presenting cells of the mammal, and a nucleic acid sequence encoding the heterologous protein, the virus being administered prior to or simultaneously with the nucleic acid sequence.

2. The method according to claim 1, wherein the virus is selected from the group consisting of adenovirus, adenovirus associated virus, retrovirus, pox virus, and vaccinia virus.

3. The method according to claim 1, wherein the virus is an adenovirus.

4. The method according to claim 3, wherein the adenovirus is selected from wild type human adenovirus, recombinant adenovirus, and fragments thereof.

5. The method according to claim 1, wherein the virus is administered prior to the nucleic acid sequence encoding the heterologous protein.

6. The method according to claim 1, wherein the virus is administered simultaneously to the nucleic acid sequence encoding the heterologous protein.

7. The method according to claim 6, wherein the virus and the nucleic acid sequence encoding the heterologous protein are simultaneously co-administered as a recombinant virus, the genome of which comprises at least one nucleic acid sequence encoding the heterologous protein.

8. The method according to claim 7, wherein the genome of the recombinant virus comprises at least regulatory sequences necessary to direct the expression of the heterologous protein in at least one antigen presenting cell of the mammal.

9. The method according to claim 8, wherein the regulatory sequences comprise promoter sequences selected from the group consisting of cytomegalovirus early promoter (CMV IEP), Rous sarcoma virus long terminal repeat promoter (RSV LTR), myeloproliferative sarcoma virus long terminal repeat (MPSV LTR), simian virus 40 early promoter (SV40 IEP), and major late promoter of the adenovirus.

10. The method according to claim 1, further comprising administering an additional virus, wherein the additional virus is the same as or different than the virus.

11. The method according to claim 1, further comprising administering an additional nucleic acid sequence encoding the heterologous protein, wherein the additional nucleic acid sequence is the same as or different than the nucleic acid sequence.

12. The method according to claim 1, further comprising administering the heterologous protein.

13. The method according to claim 1, wherein the heterologous protein or a fragment thereof is selected from the group consisting of proteins that are presented by a class I major histocompatibility molecule (CMH I), a class II major histocompatibility molecule (CMH II), or both a class I major histocompatibility molecule and a class II major histocompatibility molecule.

14. The method according to claim 1, wherein the heterologous protein is selected from the group consisting of secreted proteins, membrane proteins, receptors, intracellular proteins, and nuclear proteins.

15. The method according to claim 14, wherein the secreted protein is selected from the group consisting of neuromediators, hormones, interleukines, lymphokines, interferons, chemokines, and growth factors.

16. The method according to claim 1, wherein the mammal is selected from the group consisting of mouse, rat, rabbit, hamster, pig, cow, goat, sheep, horse, and primate.

17. The method according to claim 1, wherein the administration of the virus and the nucleic acid sequence encoding the heterologous protein is performed via one or more techniques selected from the group consisting of intravenous injection, intravaginal injection, intrarectal injection, intramuscular injection, and intradermic injection.

18. The method according to claim 17, wherein the intravenous injection is performed by retro-orbital sinus injection, tail injection, hepatic injection, femoral injection, or jugular injection.

19. A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein, comprising:
administering to the mammal a recombinant virus, the genome of which comprises at least a nucleic acid sequence encoding the heterologous protein and regulatory sequences, in an amount sufficient to deplete or inhibit at least some antigen presenting cells of the mammal; and
optionally administering a virus or a fragment thereof, the genome of which does not express the heterologous protein.

20. The method according to claim 19, further comprising administering a virus or a fragment thereof, the genome of which does not express the heterologous protein.

21. The method according to claim 19, further comprising administering a nucleic acid sequence encoding the heterologous protein.

22. The method according to claim 19, further comprising administering the heterologous protein.

23. The method according to claim 19, wherein the mammal is a mouse and the recombinant virus is a recombinant adenovirus.

24. The method according to claim 23, wherein the amount of adenovirus administered to deplete or inhibit at least some antigen presenting cells of the mouse is equal or greater than about 4×10^{10} particles, including the optionally administered virus or a fragment thereof, the genome of which does not express the heterologous protein.

25. The method according to claim 23, wherein the amount of adenovirus administered to deplete or inhibit at least some antigen presenting cells of the mouse is equal or greater than about 6×10^{10} particles, including the optionally administered virus or a fragment thereof, the genome of which does not express the heterologous protein.

26. The method according to claim 24, wherein the amount of the adenovirus able to form plaques, is equal or greater than about 4×10^{9} pfu/mouse.

27. A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein, the method comprising:

(i) Optionally, co-administering to a first mammal, at least one virus and a nucleic acid sequence encoding the heterologous protein, the virus being administered simultaneously, sequentially or separately with the nucleic acid sequence, and determining at least one amount of the heterologous protein and the virus, sufficient to trigger an immune response against the heterologous protein by the first mammal; optionally, re-performing step (i) until the amount is determined;

(ii) co-administering to a second mammal the nucleic acid sequence encoding the heterologous protein, in an amount sufficient to trigger an immune response against the heterologous protein, as determined at step (i) and prior to or simultaneously administering the virus, in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against the virus and sufficient to deplete or inhibit at least some antigen presenting cells of the mammal, and determining for the second mammal at least one amount of the virus that reduces and/or suppresses the anti-heterologous protein immune response in the mammal; and re-performing step (ii) until the amount is determined; wherein the nucleic acid sequence encoding the heterologous protein is co-administered to the mammal prior to or simultaneously with a virus in an amount equal to or greater than the one determined at step (ii), and wherein the mammal produces neutralizing antibodies against the virus but produces no or few neutralizing antibodies against the heterologous protein.

28. The method according to claim 27, wherein the amount of the virus of step (ii) is at least twice the amount of the virus determined at step (i).

29. The method according to claim 27, wherein the virus is selected from the group consisting of adenovirus, adenovirus associated virus, retrovirus, pox virus.

30. The method according to claim 27, wherein the virus is an adenovirus.

31. The method according to claim 27, wherein the virus and the nucleic acid sequence encoding the heterologous protein are simultaneously co-administered as a recombinant virus, the genome of which comprises at least the nucleic acid sequence encoding the heterologous protein.

32. The method according to claim 27, further comprising administering the heterologous protein.

33. The method according to claim 27, wherein the nucleic acid sequence encodes human thrombopoietin.

34. The method according to claim 33, wherein the nucleic acid expresses human thrombopoietin under the control of the RSV promoter (AdRSVhuTPO).

35. A method of inhibiting in a mouse formation of neutralizing antibodies directed against an heterologous protein, the method comprising:

(i) optionally, administering to a first mouse, a recombinant adenovirus, the genome of which comprising at least a nucleic acid sequence encoding the heterologous protein, and determining the amount of recombinant adenovirus particles that triggers an immune response against the heterologous protein in the mouse without depleting or inhibiting at least some antigen presenting cells of the mouse, wherein:

(a) the amount of recombinant adenovirus particles is below 4×10^{10} particles, and/or

(b) the amount of the adenovirus particles able to form plaques is below 4×10^{9} pfu/mouse;

and optionally, re-performing step (i) until the amount is determined;

(ii) administering to a second mouse an amount of recombinant adenovirus particles in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against the recombinant adenovirus particles and sufficient to deplete or inhibit at least some antigen presenting cells of the mouse, and determining for the second mouse at least one amount of the recombinant adenovirus particles that reduces and/or suppresses the anti-heterologous protein immune response in the mouse, wherein :

(a) the amount of recombinant adenovirus particles is at least equal to or greater than 4×10^{10} particles, and/or

(b) the amount of the adenovirus particles able to form plaques is equal to or greater than 4×10^{9} pfu/mouse;

and optionally re-performing step (ii) until the amount is determined;

wherein when one administers to the mouse the recombinant adenovirus particles in an amount equal to or greater than the one determined at step (ii), the mouse produces neutralizing antibodies against the adenovirus but produces no or few neutralizing antibodies against the heterologous protein.

36. The method according to claim 35, wherein the amount of the recombinant adenovirus particles of step (ii) is at least twice the amount of the recombinant adenovirus particles determined at step (i).

37. The method according to claim 35, further comprising administering the heterologous protein.